REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-3, 5-19, 21-46 and 47-54 will be pending in this application. Claims 1, 11 (withdrawn), 15-16 (withdrawn) and 29 (withdrawn) have been amended to more particularly point out and distinctly claim the subject matter. The amendments to claims 11, and 15-16 merely update the claims dependencies in view of the amendments to claim 1. Claim 29 has been amended to be commensurate in scope to claim 1. Claims 47-54 are newly added. No new matter has been introduced with the foregoing claim amendments and newly added claims. Reconsideration is respectfully requested in view of the remarks below.

I. FORMALITIES

A. Interview

At the outset, Applicant and their undersigned representative wish to thank Examiner Strzelecka for the telephonic interview held on November 16, 2009. During this interview, a number of issues were clarified which have helped Applicant more clearly understand the Examiner's position and to present the below arguments to overcome the rejections. Applicant thanks Examiner Strzelecka for her time and the courtesy of extending the interview.

B. Support for the Amendments and New Claims

Support for the amendments and newly added claims are found throughout the application as originally filed. More particularly, support for the amendments to claims 1 and 29 is found, for example, in paragraphs 12, 55 and 58 of US Publication No. 2005/0042633 (the publication of the subject application). Paragraph 12 recites the feature of the attachment complex attaching to a solid support. The attachment complex being attached to both sides of the DNA binding cleft is recited, for example in paragraph 55 and FIG. 2. Paragraph 58 recites, for example, family A and family B polymerases.

Claim 47 finds support, for example, in paragraph 54 wherein the attachment complex (e.g., anchors) are covalently attached to the polymerase. Claim 48 finds support, for example, in Figure 2 and paragraph 55. Claims 49-51 find support, for example, in paragraph 55. Claims 52-53 find support, for example, in paragraph 65. Claim 54 finds support, for example, in Example 9.

In view of the foregoing support, no new matter has been entered with the foregoing amendments and newly added claims. Accordingly, Applicant respectfully requests that they be entered.

C. Family A and Family B polymerases

Applicant has amended claims 1 and 29 to specifically recite family A and family B polymerases. Support is found, for example, in paragraph 58. Applicant elected family B polymerases in the original species election (e.g., claim 20). However, as explained more fully below, the domains of family A and family B polymerases have a common overall architecture, which resembles a right hand and consists of 'thumb,' 'palm' and 'fingers' domains. The palm domain contains the active site and this portion shows a high degree of structural similarity between the two families. Due to this high degree of structural similarity, it is believed that remarks and arguments are applicable to both families. As such, Applicant respectfully requests that the Examiner enter this subject matter into the application.

D. Rejoinder

Under M.P.E.P. § 821.04, if Applicant elects claims directed to the product, and the product claims are allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claims must be rejoined. Process claims, which depend from, or otherwise include all the limitations of the patentable product, will be entered as a matter of right. In view of the amendments and remarks, Applicant submits that all the claims are allowable. Accordingly, Applicant respectfully requests that the Examiner enter all the claims.

II. REJECTION UNDER 35 U.S.C. § 102(a)

The Examiner has maintained the rejection of claims 1-3, 18-19 and 26 under 35 U.S.C. § 102 as allegedly being anticipated by Motz *et al.*, *JBC* vol. 277, No. 18, 16179-16188, 2002 ("Motz *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

Under MPEP § 2131:

> [a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In order to expedite allowance of the present application, Applicant has amended the claims to clearly distinguish Motz *et al.* In the present claims, the attachment complex is attached to the polymerase and to a support. Motz *et al.* in no way teach a support. As such, there is no anticipation. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

III. FIRST REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 19 and 22 under 35 U.S.C. § 103(a) as allegedly being obvious over Motz *et al.* and U.S. Patent No. 5,198,543 ("Blanco *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

Again, Applicant has amended the claims to clearly distinguish Motz *et al.* Blanco *et al.* do not supply the deficiencies of the primary reference. Blanco *et al.* do not teach or even suggest an attachment complex, nor a support. Blanco *et al.* teach a modified $\phi 29$ polymerase with a modified exonuclease activity. In the present claims, the attachment complex is attached to polymerase and to a support. Motz *et al.* in no way teach a support. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

IV. SECOND REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claim 23 as allegedly being obvious over U.S. Patent No. 6,255,083 ("Williams") and Motz *et al.* To the extent that the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

Williams does not teach or suggest an attachment complex that attaches the polymerase to a support and irreversibly associates a target nucleic acid with the polymerase until replication is complete.

Motz *et al.* do not supply the deficiencies of the primary reference. Motz *et al.* in no way teach the foregoing features, nor suggest their modification. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

V. REJECTION UNDER 35 U.S.C. § 112, Written Description

Claims 1-3, 18, 19, 22, 23 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the written description requirement. The Examiner alleges that the claims read on any polymerase and there is insufficient written description in the specification to support broad claims. To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

Under MPEP § 2163 II. A. 1 ii):

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus,

> when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." (citations).

Applicants have amended the claims to include only "family A" and "family B" DNA-dependent DNA polymerases. As recited in paragraph [0058]: Family A polymerases include for example, Klenow, Taq, and T7 polymerases. Family B polymerases include for example, the Therminator polymerase, phi29, RB-69 and T4 polymerases. As such, family A & B polymerases are adequately described in the specification.

FIG. 2 and paragraph 54 of the subject publication specifically disclose the 9°N polymerase and its attachment complex attached to the polymerase at positions K53 and K229 (Therminator positions). These two positions straddle the DNA binding cleft as is shown in FIG. 2. Therminator and 9 °N are both family B polymerases.

In this regard, the Examiner's attention is respectfully drawn to the enclosed journal reference Rodriguez *et al.* (Rodriguez *et al.*, *JMB* 299(2): 447-462, enclosed with Supplemental Information Disclosure Statement), which reference teaches the high resolution crystal structure of a 9°N DNA polymerase. In specifically discussing the palm domain which comprises the active site, Rodriguez *et al.* state:

> The palm, which contains the active site for polymerization, shows a high degree of structural similarity to the palm subdomain of other DNA polymerases. It is as structurally similar to pol I family polymerases as to those of the pol a family. Its rms deviation from RB69 pol around the active site (blue region in Figure 4(b)) is 0.84 Å (26 C^{α} atoms).

In other words, after analyzing the crystal structure of 9°N, Rodriguez *et al.* state that the palm region of 9°N is as structurally similar to pol I family polymerases as to those of the pol a family polymerases (family A and family B).

Applicant submits that claims 1 and 29 are adequately described and satisfy the written description requirement. For example, a representative number of family A species and

family B species are recited in the specification. In addition, from the crystal structure point of view, there is a high degree of structural similarity between the palm domains of family A polymerases and family B polymerases.

In addition, the claims recite that the attachment complex attaches the polymerase on both sides of the DNA binding cleft and also attaches the polymerase to a support. The claimed polymerases are thus adequately described in the specification (*e.g.*, FIG. 2).

Under MPEP § 2163, the palm domain of family A and family B are adequately described as there is a high degree of structural similarity within their palm domains. This *insubstantial variation* between the palm domains of A & B families ensures that the written description requirement is satisfied. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

VI. REJECTION UNDER 35 U.S.C. § 112, Enablement

Claims 1-3, 18, 19, 22, 23 and 26 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

In Applicant's responses of May 11, 2009 and April 30, 2007, *Wands* analyses were included in a sincere effort to overcome an alleged enablement rejection. In those responses, Applicant included the following factors: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Applicant submits that given the detailed teachings and guidance of the instant specification, one of skill in the art, namely a molecular or structural biologist, would know how to construct a family A or B polymerase having an attachment complex that attaches to the polymerase on both sides of the DNA binding cleft as is currently taught and claimed. This is

due to the fact that family A and B polymerases have highly structurally related DNA binding clefts. The conserved structural architecture of a DNA polymerase's DNA binding cleft is commonly referred to as resembling a 'right hand,' consisting of 'thumb,' 'palm,' and 'finger' domains. As such, given the detailed guidance, one of skill in the art would know where to position an attachment complex that attaches to the polymerase on both sides of the conserved DNA binding cleft.

As evidence of the conserved structural architecture between the DNA binding clefts of family A and B DNA polymerases, Applicant provides herewith several review articles published prior to the filing date of the instant application, which discuss in detail the structural conservation among various DNA polymerase families. First, Doublié *et al.* (*Structure*, 1999 Feb 15;7(2):R31-5; enclosed with Supplemental IDS) provide a discussion of the structures of four polymerases from different families, namely Taq (Family A), T7 (Family A), polβ (Family X), and HIV-1 reverse transcriptase (Family RT). Doublié *et al.* state:

> The structural portraits of polymerases from all four families have revealed similar silhouettes, featuring a U-shaped DNA-binding cleft that resembles a partially opened right hand with 'fingers', 'thumb', and 'palm' subdomains, as was originally described for the large fragment of *Escherichia coli* DNA polymerase I (Klenow fragment). [See, column 1 on page R31; citation omitted].

Similarly, Albà (*Genome Biol.* 2001;2(1); enclosed with Supplemental IDS), compares the crystal structures of T7 (Family A) and Tgo (Family B) polymerases (*see*, Figure 2 found on page 3), and concludes:

> The catalytic domains of type A and B DNA polymerases have a common overall architecture, which resembles a right hand and consists of 'thumb', 'palm' and 'fingers' domains (Figure 2a,b). ...The most conserved region is their palm domain, which contains the catalytic site. [See, column 2, page 2, first full paragraph; citation omitted].

Finally, Steitz (*J Biol Chem.* 1999 Jun 18;274(25):17395-8; enclosed with Supplemental IDS), compares Taq (Family A), RB69 gp43 (Family B), polβ (Family X), and HIV-1 reverse transcriptase (Family RT) polymerases (*see*, Figure 1 found on page 17396), also

concludes that the DNA binding cleft of polymerases from different families share a common architecture. Specifically, Steitz states:

> Independent of their detailed domain structures, all polymerases whose structures are known presently appear to share a common overall architectural feature. They have a shape that can be described as consisting of "thumb." "palm," and "fingers" domains. [See, paragraph bridging columns 1 and 2 on page 17395; citation omitted].

As evidenced above, the structural conservation of the 'right hand' architecture of family A and B polymerase DNA binding clefts was well known at the time of filing the instant application. Accordingly, Applicant submits that one of skill in the art would know how to construct both family A and family B polymerases having attachment complexes that attach to the polymerase on both sides of the DNA binding cleft without undue experimentation.

With respect to claim scope, Applicant has narrowed the claims by reciting only family A & family B polymerases. The specification recites specific species of such polymerases, namely, for family A polymerases, Klenow, Taq, and T7 polymerases are recited. For family B polymerases, Therminator polymerase, phi29, RB-69 and T4 polymerases are recited.

In the current specification at paragraphs 54-55 and FIG. 2, there is a detailed discussion of an the attachment complex with a structural model comprising a 9 Degrees North DNA polymerase. The polymerase comprises anchors inserted at Therminator amino acid positions K53 and K229, respectively. The anchors are identical in amino acid sequences. These two positions straddle the DNA binding cleft as shown in FIG. 2.

In Applicant's response dated May 11, 2009, the inventor's published scientific journal was brought to the Examiner's attention *i.e.*, JGK Williams *et al.*, *Nucleic Acid Research* 2008, Vol. 36, No. 18, pp 1-11. On page 2 of the reference, the authors state the following:

> In this report, we describe an artificial processivity complex that *both traps the template DNA on the polymerase and facilitates oriented immobilization on biotinylated surfaces*. Starting with the parent polymerase (above) adapted to phosphate-labeled dNTPs, we inserted AviTag™ peptide 'legs' at two surface-exposed

> locations flanking the DNA-binding cleft. The AviTag peptides provide highly specific sites for enzymatic biotinylation of the polymerase by E. coli biotin–protein ligase. Processivity is enhanced with streptavidin binding the AviTag legs, retaining the template in the DNA-binding cleft. We show that the template DNA is stably associated with the polymerase, and that the polymerase–DNA–streptavidin complexes are active both in solution and when immobilized on biotinylated coverglass surfaces. *We demonstrate that the clamp converts a naturally nonprocessive DNA polymerase into a highly processive one capable of incorporating thousands of nucleotides without dissociating from the template.* [Emphasis added].

The foregoing reference unequivocally demonstrates that the claimed invention works. The anchor and attachment complex as claimed *converts a naturally nonprocessive DNA polymerase into a highly processive one capable of incorporating thousands of nucleotides without dissociating from the template.* This reference demonstrates that the claimed invention is fully enabled.

Moreover, on page 2 of the JGK Williams *et al.*, *Nucleic Acid Research* paper under the heading of "Polymerase AviTag constructs," the following is set forth:

> The starting enzyme was a mutant of Therminator DNA polymerase (http://www.neb.com) adapted by directed evolution for efficient utilization of phosphate-labeled nucleotides manuscript in preparation). AviTag is a peptide substrate for E. coli biotin–protein ligase which, when fused to a target protein, provides a site for efficient enzymatic biotinylation (http://www.avidity.com). The overlapping primer PCR method of Chiu et al. (27) *was used to insert AviTag in the mutant polymerase at two positions (Therminator coordinates K53-V54 and K229-F230). The 21-amino acid insertion ssGLNDIFEAQ KIEWHEgass comprises AviTag (upper case) flanked by arbitrarily chosen amino acids (lower case)*; enzymatic biotinylation occurs at the epsilon-amine of the lysine (K). The starting plasmid was a 6.4-kb pBAD-HisC plasmid (Invitrogen) containing the mutant polymerase gene. [Emphasis added].

Given the detailed guidance in the specification and the clear knowledge of the state of the art and homology of polymerases' active site, Applicant believes that one of ordinary

skill in the art can practice the invention as presently claimed according to the requirements of 35 U.S.C. §112, first paragraph. Accordingly, Applicant respectfully requests that the above rejection be reconsidered and withdrawn.

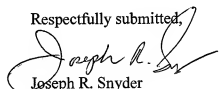
VII. REJECTION UNDER 35 U.S.C. § 112, Written Description

The Examiner has rejected claims 1-3, 18, 19, 22, 22 and 26 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleged that certain of the previous amendments to claim 1 constituted new matter.

In an effort to expedite prosecution in the present application, Applicant has amended claim 1. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection. In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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